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Pharmacokinetics-Pharmacodynamics relationship of Succinylcholine and Rocuronium during Electroconvulsive Therapy

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To be submitted

ABSTRACT

Background

Neuromuscular blocking agents (NMBAs) are used during electroconvulsive therapy (ECT) to mitigate the induced severe muscle contractures. The objective of this study was to analyze the pharmacokinetics-pharmacodynamics (PK-PD) relationship of succinylcholine and rocuronium during ECT.

Methods

The available data on the first twitch height (T1) of 31 patients who underwent ECT as well as the corresponding intravenously applied doses of succinylcholine and rocuronium were used for the analyses in the study. The T1% (percentage change from the response to the supramaximal stimulus) derived from continuously applied TOF Watch recording to assess the minimal effective doses of succinylcholine and rocuronium during ECT. NONMEM software was used to construct, evaluate and validate the PKPD models. The PKPD of the two NMBAs was described using a two-compartment PK model and effect compartment model. The PK-PD parameter estimates required for the simulation of blood concentration were abstracted from previously reported studies in the literature.

Results

The PD model parameter estimates for succinylcholine and rocuronium during ECT were $k_{e0} = 0.04 \text{ min}^{-1}$ (SEE=0.004) and $k_{e0} = 0.17 \text{ min}^{-1}$ (SEE=0.19), respectively. The Ce50 estimations for these two NMBAs were amounted to 0.7 $\mu\text{g/ml}$ (SEE=0.06) and 1.6 (SEE=0.1), respectively. The k_{e0} for neostigmine was not estimable, however the Ce50 was measured to be 0.412 (SEE=0.06).

Conclusion

The estimated PK-PD parameters for succinylcholine and rocuronium during ECT are almost comparable to previous PK-PD estimates for these two NMBA. The observed higher Ce50 for rocuronium might explain faster recovery after ECT from NMB and warrants further investigation.

INTRODUCTION

Neuromuscular blocking agents (NMBAs), known as muscle relaxants, are key medications administered to patients undergoing electroconvulsive therapy (ECT). The induced relaxation using NMBAs averts ECT patients' unwanted severe muscular responses that might result in physical injuries such as bone fractures and unpleasant experience of the procedure.¹ These drugs also modify the quality and duration of induced seizure by ECT that has been shown to be associated with the efficacy of ECT. Anesthetic drugs and neuromuscular blocking agents (NMBAs) are administered to ensure patient comfort and safety, but need also be titrated to provide optimal conditions for the induced seizure activity during the treatment, while allowing a rapid recovery upon its completion.²

Succinylcholine (SUX) is a bis-quaternary ammonium compound and depolarizing neuromuscular blocking agent, has been extensively used in anesthesia of ECT. In patients without plasma cholinesterase deficiency, succinylcholine has the advantage of a rapid onset and short duration of action. Therefore, this NMBA is preferred as the main NMBA for inducing muscle relaxation during ECT.¹ In spite of common use of succinylcholine, there are medical conditions that succinylcholine do not serve as a safe NMBA an alternative NMBA might be required for the safety of patients. Succinylcholine is hydrolyzed by plasma cholinesterase.³ Genetic variants of the plasma cholinesterases, low plasma cholinesterase activity due to an acquired deficiency (e.g. liver disease, carcinoma, debilitating disease), and other factors, among which some remain unknown, may lead to an episode of prolonged apnea after succinylcholine.³ Because of this recognized variation in the activity of plasma cholinesterases, large intersubject differences in pharmacokinetic, pharmacodynamic, and pharmacokinetic–pharmacodynamics relations are expected.⁴

Currently, nondepolarizing NMBAs such as rocuronium bromide are being used as an alternative choice for inducing muscle relaxation during ECT. Rocuronium bromide is an aminosteroid non-depolarizing neuromuscular blocking agent with a more rapid action than other currently available non-depolarizing drugs but with duration of action considerably longer than succinylcholine vecuronium. Rocuronium acts by competing for cholinergic receptors at the motor endplate.⁵

The nondepolarizing NMBAs have longer duration of action and should be used along with reversal agents (e.g. neostigmine) to accelerate recovery from neuromuscular blockade (NMB) and prevent postoperative residual NMB. The use of anticholinesterases to reverse residual neuromuscular block is efficacious only if recovery is already established. Even in these circumstances, the full effect of anticholinesterases and recovery takes considerable

time to achieve.^{6,7} Neostigmine is a parasympathomimetic which by indirect cholinomimetic mechanism inhibits acetylcholinesterase, thereby increasing the concentration of acetylcholine in the synaptic cleft.

Hypothetically, the ideal reversal agent can be given at any time after the administration of a NMBA and completion of ECT, and is efficacious irrespective of the degree of neuromuscular blockade. It has ideally a rapid onset of action and a minimal side effect profile.^{6,7} Similarly, an ideal nondepolarizing NMBA could be an agent with short duration of action and recovery time with potentially matched with a reversal agent that could be applied at any time after achieving the desired level of neuromuscular blockade. The search for the ideal nondepolarizing NMBA involves an understanding of the factors that makes succinylcholine blockade so evanescent. This entails increasing our knowledge on pharmacology of succinylcholine and other nondepolarizing NMBAs, i.e. simultaneous measurement of their plasma concentrations or a surrogate measure (pharmacokinetics) and neuromuscular blockade (pharmacodynamics). A pharmacokinetic–pharmacodynamic analysis could help in measuring the drug effect and the relation between blood concentration and the target organ under the effect of drug.

ECT produces hemodynamic changes, including increase in cardiac output (CO) during seizure activity due to sympathetic stimulation and systemic catecholamine surges.¹ Effect of cardiac output on pharmacokinetics of has been investigated. To our knowledge there is no study in literature to include the pharmacokinetic–pharmacodynamics (PK-PD) relations/analysis of succinylcholine and an alternative such as rocuronium during ECT. The objective of this study was to provide a quantitative model to describe the kinetics and the dynamics of succinylcholine chloride and rocuronium after the different bolus doses applied for inducing muscle relaxation in patients underwent ECT. Accordingly, the aims in model development were to establish the PK–PD model for succinylcholine and rocuronium induced NMB in patients undergoing ECT. The secondary objective was to determine if the in vitro rate of degradation recorded by neuromuscular transmission monitoring (NMT) is of predictive value for the in vivo elimination rate of succinylcholine and rocuronium in ECT patients.

MATERIALS AND METHODS

This study is a secondary analysis on the crossover randomized controlled, assessor blinded clinical trial that was conducted in the post-anesthesia care unit at Massachusetts General Hospital in Boston, MA, USA to estimate the optimal doses of rocuronium and succinylcholine for ECT. The results of the main study are presented in chapter three of this dissertation.

Study population

Two hundred and twenty-seven ECT sessions were conducted in 45 hospitalized patients aged 24-80 years with American Society of Anesthesiologist Class I -III, admitted for a series of ECT treatments at a frequency of 3 times per week. The indication for ECT in all enrolled patients was major depressive disorder or bipolar disorder, and all patients were taking psychotropic medications including antidepressants and antipsychotics, as indicated by their psychiatric condition. Only patients within 20% of the ideal body weight were included. Exclusion criteria included an age of <18 years, patients with illness or medications known to influence neuromuscular transmission, significant renal or liver dysfunction, electrolyte abnormalities and pregnant women.

Protocol

The flow of patients through the study is depicted in figure 1. Following screening by the psychiatrist and anesthesiologist responsible for the clinical treatment of each patient, informed consent was obtained and patients were enrolled. After preoxygenation with 100% oxygen for 3 minutes through a facemask, anesthesia was induced with propofol (1.2 mg.kg⁻¹ intravenously over 5 sec). Continuous neuromuscular transmission monitoring was applied after stabilization and baseline calibration to establish a control twitch response prior to NMBA injection (see below). Succinylcholine (Quelicin[®], Hospira Inc., Lake Forest, IL) 0.8 (2.67 × ED₉₅) mg.kg⁻¹ or rocuronium-bromide (Zemuron[®], Oganon USA Inc) 0.4 mg.kg⁻¹ (1.33 × ED₉₅) was then administered intravenously over 5 sec via an intravenous catheter in the arm contralateral to the side of neuromuscular transmission monitoring, which was then flushed with a 10 ml bolus of normal saline. These initial doses were selected as the median of applied succinylcholine and rocuronium doses to achieve acceptable ECT induced motor activity in pilot study of 10 patients. Ventilation was assisted until recovery of normal spontaneous ventilation via a facemask and an Ambu-bag with supplemental 100% oxygen. After the peak effect of neuromuscular transmission blockade was established, an electrical stimulus at approximately 6x seizure threshold was delivered with right unilateral application of electrodes with a MECTA Model SR II apparatus (MECTA Corp., Portland, OR, USA). The treating psychiatrists, blinded to the type and dose of the NMBA determined the stimulus parameters for the applied ECT (level, dynamic, energy, intensity and duration of stimulus) and the subsequent duration of seizure. Systolic and diastolic blood pressures (SBP and DBP) were recorded every 3 min and the heart rate (HR), and oxygen saturation (SpO₂) were monitored and recorded continuously throughout the procedure and until full recovery. Temperature was monitored and maintained ≥ 35°C. Labetalol (10-50 mg IV) or esmolol (40-80 mg IV) was administered to treat hypertension and tachycardia, when necessary.

After termination of seizure and when appropriate, as determined by the practicing anesthesiologist, the rocuronium-induced neuromuscular blockade was reversed with neostigmine 50 microgram.kg⁻¹, administered with glycopyrrolate 10 microgram.kg⁻¹.⁸ After return of normal spontaneous breathing, patients were placed in a lateral decubitus position. Neuromuscular monitoring was continued until full recovery of the neuromuscular blockade was recorded (T1 =100% or TOF ratio of >0.9 for succinylcholine and rocuronium, respectively).⁹

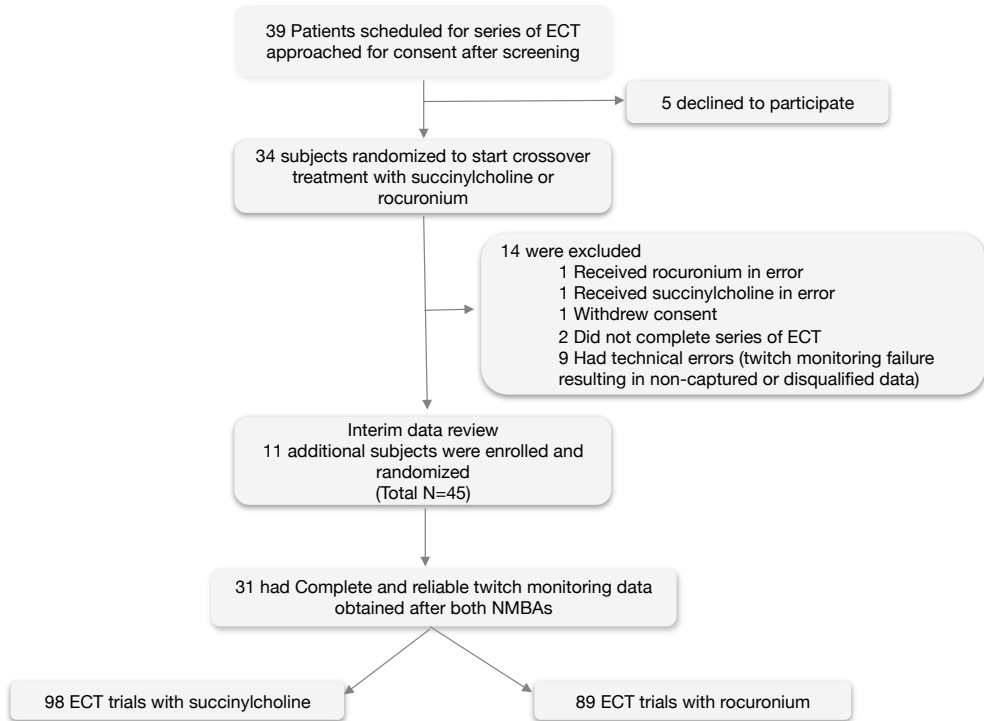


Figure 1. Patient flow through the study

Neuromuscular transmission monitoring

Neuromuscular transmission was monitored using acceleromyography and a TOF-Watch SX® monitor (Organon, Roseland, NJ, USA) connected to a laptop computer. Before induction of anesthesia, the subject's arm was taped in a stable and comfortable position, skin was cleansed and surface electrodes were placed (3-5 cm apart) over the ulnar nerve at the wrist. A hand adaptor (Organon International Inc., Roseland, NJ, USA) was used to fix the thumb position to minimize the potential variability in evoked muscle contraction. The TOF-

watch was calibrated by using the standard calibration with default supramaximal stimulation (CAL1: 10 sec stimulation current of 50 mA), and ulnar nerve stimulation was resumed with single twitch stimulation at 0.1 Hz and continued till observation of less than 5% variation of twitch heights for 2-3 min, after which a bolus dose of the NMBA was injected.¹⁰ The same mode of stimulation was continued until the peak effect of neuromuscular transmission blockade was established (first of three consecutive twitches with the same/increasing value or $\geq 95\%$ depression of twitch).¹⁰ After completion of the ECT-induced seizure, twitch stimulation was continued in patients who had received succinylcholine until a twitch height of 100% of control (baseline) with response variation less than 5% for 2 min was recorded.¹⁰ For rocuronium-treated patients the mode of stimulation was changed to TOF-stimulation with square wave pulses of 0.2 msec duration delivered at 2 Hz every 15 sec, and continued until three consecutive responses with a TOF ratio ≥ 0.9 were recorded. All twitch height values during the recovery phase were normalized to final twitch value, and were expressed as percentages of control values.¹⁰

NMBA randomization and crossover

Patients were randomized to receive either succinylcholine or rocuronium at a standard initial dose, as listed above, during their first ECT. During each subsequent ECT treatment (two days apart), patients received a 10% higher (if insufficient paralysis) or lower (if sufficient or excessive paralysis) dose of the same NMBA until the *minimum effective dose* that resulted in acceptable muscle relaxation (defined as the *individual optimal dose*) was identified. When the optimal dose of the first NMBA was identified, each patient received the second NMBA (i.e. succinylcholine if rocuronium had been administered, and vice versa) for his or her subsequent ECT treatments, and the dose was increased or decreased in 10% increments according to the same protocol until the minimum acceptable dose for the second NMBA was established.

Quality assessment of muscle relaxation

The quality of muscle relaxation during seizure was independently assessed using a dichotomous scale of 'acceptable' or 'not acceptable' by two psychiatrists, who were blinded to the dose and type of NMBA. A grading system was used to score the two psychiatrists' evaluation. Each psychiatrist provided a single score based on defined criteria for 'acceptable' or 'not acceptable' ECT conditions (Table 1, chapter three). A summed score of more than or equal to two was considered as 'acceptable' level of induced muscle relaxation. Any summed score of less than two was considered as 'not acceptable' level of induced muscle relaxation. Consequently, NMBA trials were continued until the lowest dose that provided acceptable relaxation during induced seizure was identified.

Outcome variables for PK-PD analysis

The primary clinical outcome of the main study (chapter three) was to define the optimal effective dose (OED) of succinylcholine and rocuronium for each subject to achieve acceptable level of muscle relaxation, defined as the smallest dose of succinylcholine or rocuronium that resulted in adequate muscle relaxation and safe application of ECT in 50% of the cases (OED₅₀).

The secondary outcome of main study was the duration of the neuromuscular transmission blockade, defined as the time to complete recovery from neuromuscular blockade after a single bolus dose of the OED₅₀, i.e. return of the first twitch height to its baseline for both if succinylcholine and succinylcholine and additional measure of TOF ratio ≥ 0.9 if rocuronium was used. To evaluate the secondary outcome of the primary analysis, all patients were monitored until full recovery from neuromuscular blockade (twitch height of 100% or TOF ratio ≥ 0.9 for succinylcholine and rocuronium, respectively). Using this data and for pharmacokinetic–pharmacodynamics (PK–PD) analysis in this study, we extracted all the measured first twitched (T1s) changes during the NMBA onset of action and recovery from the induced neuromuscular blockade (NMB), corresponding to the applied doses (both optimal and suboptimal doses). Accordingly, we generated two data sets for PK-PD analysis including the T1 changes in response to all the applied succinylcholine and rocuronium doses, respectively. Additionally, the measured OED₅₀s of succinylcholine (0.85 mg/kg) and rocuronium (0.41 mg/kg) and the corresponding T1 suppression for acceptable motor activity during ECT were used to compare the onset of action and recovery times for succinylcholine, rocuronium and rocuronium plus neostigmine.

The primary objective of this study was to provide a quantitative model to describe the PK-PD relationship of succinylcholine chloride and rocuronium applied doses in patients undergoing ECT. The secondary objective was to determine if the in vitro rate of degradation (T1) is of predictive value for the in vivo elimination rate of succinylcholine and rocuronium in the patient that underwent ECT procedure. Subsequent aims in model development were to establish the PK–PD model for rocuronium-induced NMB and its reversal by neostigmine.

Statistical analysis

The data were analyzed using the statistical package NONMEM, Version 7.3.0 (Icon Development Solutions, Hanover MD, USA). Pharmacodynamic parameters were assumed to be log-normally distributed across the population. Residual error was assumed to be normally distributed, but the dependent variable was constrained to lie within the interval (0, 100). The Laplacian approximation was used for the estimation method.¹¹ The generalized additive model (GAM) procedure was used to identify covariates.¹² The GAM procedure

is a multiple nonlinear regression analysis of the empirical Bayes estimates for each of the pharmacodynamic parameters and the available covariates.¹² To assess goodness-of-fit, the coefficient of determination (R^2 , figure 2) was calculated for every occasion and was used as a measure of the goodness of fit of the regression model (figure 2A and B).

Pharmacodynamic modeling

The pharmacokinetic models were coupled to an inhibitory sigmoid E_{\max} model via a blood-effect-site concentration half-life $t_{1/2}k_{e0}$ ($t_{1/2}k_{e0}$: the half time of equilibration between drug concentration in the blood and drug effect; k_{e0} : the effect compartment equilibration rate constant). For neostigmine it was assumed that it increases the effect compartment concentration at 50% blockage representing (Ce_{50} , the effect-site concentration associated with 50% maximal drug effect that often referred as the potency factor) of rocuronium with

$$Ce_{50_{rocneo}}(t) = Ce_{50_{roc}} \cdot (1 + (Ce_{neo}(t) / Ce_{50_{nreo}})^{Y_{neo}}).$$

The concentration in the effect compartment,

$Ce(t)$ is given by $dCe(t) / dt = k_{e0} \cdot (Cb(t) - Ce(t))$ where $Cb(t)$ is the blood concentration of the NMB agent or the antagonist, and $k_{e0} = \log(2) / t_{1/2}k_{e0}$. For neostigmine, not all parameters were identifiable; and an indirect response model to describe acetylcholinesterase was deemed to be unfeasible. Therefore it was assumed that the k_{e0} of neostigmine was identical to the k_{e0} of rocuronium, and the offset of effect of neostigmine that could not be estimated from the data was removed from the model by the following formula:

$$dCe_{neo}(t) / dt = k_{e0_{roc}} \cdot Cb_{neo}(t)$$

The neuromuscular blockade is then given by:

$$\text{Effect}(t) = 100 / (1 + (Ce_{nmb}(t) / Ce_{50})^{Y_{nmb}})$$

Selection of Pharmacokinetic Parameter Sets

Because in this study no blood samples were taken, the blood concentrations of succinylcholine, rocuronium, and neostigmine were simulated using pharmacokinetic data from previously reported parameters in the literature.

1. Succinylcholine Study

Succinylcholine pharmacokinetic parameters were taken from Roy et al.⁴; the geometric means were taken from the first six subject in Table 3 of the reference with exclusion of the seventh subject as appeared to be an outlier: V1: 0.00930 L/kg, k10: 3.87, k12: 1.25, k21:

1.46 min⁻¹.

II. Rocuronium

The rocuronium pharmacokinetic parameter set was taken from Wierda et al.¹³, Table II of this reference. Vermeyen et al.'s investigation¹⁴ found this parameter set to be the best for rocuronium among the studies that investigated the parameters of interest in the literature.

III. Neostigmine

The neostigmine pharmacokinetic parameters in adults was used as investigated by Fisher et al.¹⁵, Table 2 of the reference. These constants were converted to central volume and rate constants: V1: 0.0400 L/kg, k10: 0.240, k12: 0.363, k21: 0.140, k13: 0.189, k31: 0.0201 min⁻¹.

RESULTS

Two hundred and twenty-seven ECT treatments in 45 enrolled subjects were recorded. Thirty-one subjects who completed their series of treatment and complete monitoring data for first twitches were captured, were included in the PK-PD analysis. All the NMBA doses that generated acceptable and unacceptable NMB during ECT were considered for PK-PD analysis. The mean age and body weight of the subjects were 50 ± 8 years [24-80, F/M: 15/16] and 80 ± 20 kg [49-109], respectively.

The half-life of transports between the plasma and effect compartments ($t_{1/2, k_{e0}}$) for succinylcholine and rocuronium were amounted to 17 min (SEE=1.6) and 3.7 min (SEE=3.7), respectively. Accordingly, the k_{e0} estimates were 0.04 min⁻¹ (SEE=0.004) and 0.19 min⁻¹ (SEE=0.19) for succinylcholine and rocuronium, respectively.

The estimated Ce50 for succinylcholine and rocuronium were 0.7 µg/ml (SEE=0.06) and 1.6 (SEE=0.1), respectively. For neostigmine, the constant of k_{e0} was not estimable, however, the Ce50 was estimated to be 0.412 (SEE=0.06). Table 1 (sections A and B) summarizes the parameter estimates for both succinylcholine and rocuronium/neostigmine.

Table 1. Estimated pharmacokinetic parameters for succinylcholine and rocuronium during ECT. Table 1A and 1B summarizes the measured PK-PD parameters for succinylcholine and rocuronium (reversed by neostigmine), respectively.

1A				
<i>Succinylcholine analysis</i>				
Parameter estimates	Estimate	SEE	W ²	SEE
¹ T _{1/2} k _{e0} (min)	17.1	1.58	0.261	0.0724
² Ce50 (ug/ml)	0.706	0.0599	0.221	0.05
³ Y (gamma)	35.1	3.78	0.351	0.104
⁴ SD	8.88	0.614		
1B				
<i>Rocuronium/neostigmine analysis</i>				
Parameter estimates	Estimate	SEE	W ²	SEE
Rocuronium				
T _{1/2} k _{e0} (min)	3.67	0.367	0.256	0.0131
Ce50 (ug/ml)	1.59	0.0977	0.0636	0.0128
Y	7.54	0.733	0.0875	0.0407
Neostigmine				
Ce50 (ug/ml)	0.412 2	0.06	Not estimable	
Y	3.49	0.594	0.444	0.171
SD	12.7	0.792		

1. Equilibration half-time

2. Median effective concentration

3. Gamma, determines the steepness of the concentration- effect relationship (the Hill factor describing sigmoidicity of the concentration-effect relation)

4. Standard deviation

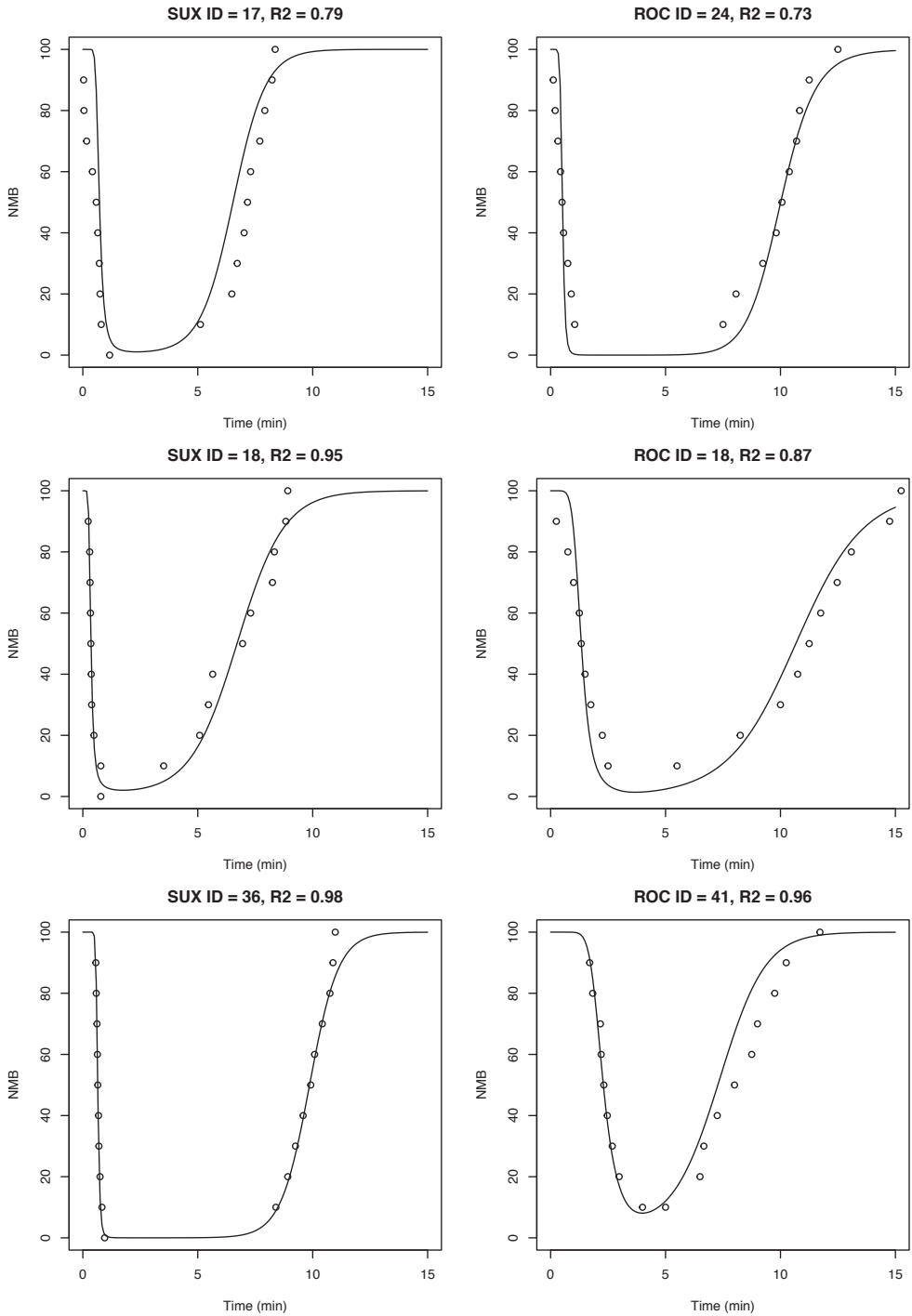


Figure 2. The plots demonstrated the examples of generated fits for individuals from data that are selected based on the range of R^2 , lowest, median and highest estimated values for succinylcholine and rocuronium studies)

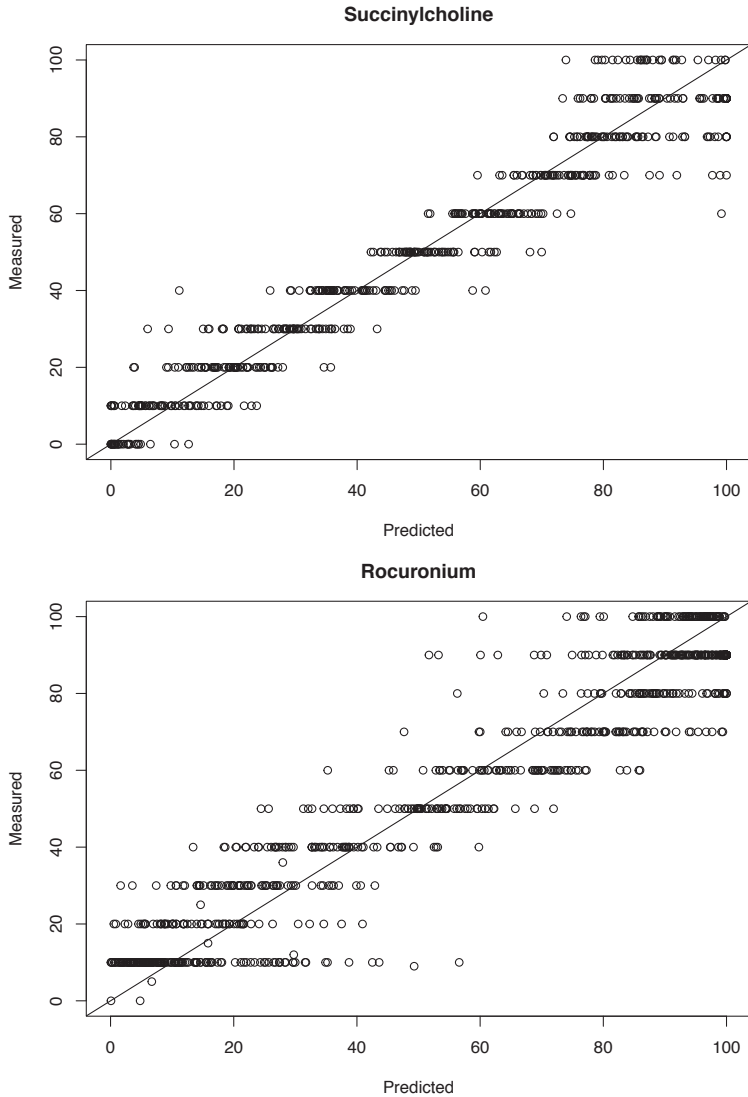


Figure 3. A and B: The graph demonstrates the goodness-of-fit plots (observed vs. predicted individual first twitch heights) for succinylcholine and rocuronium, respectively.

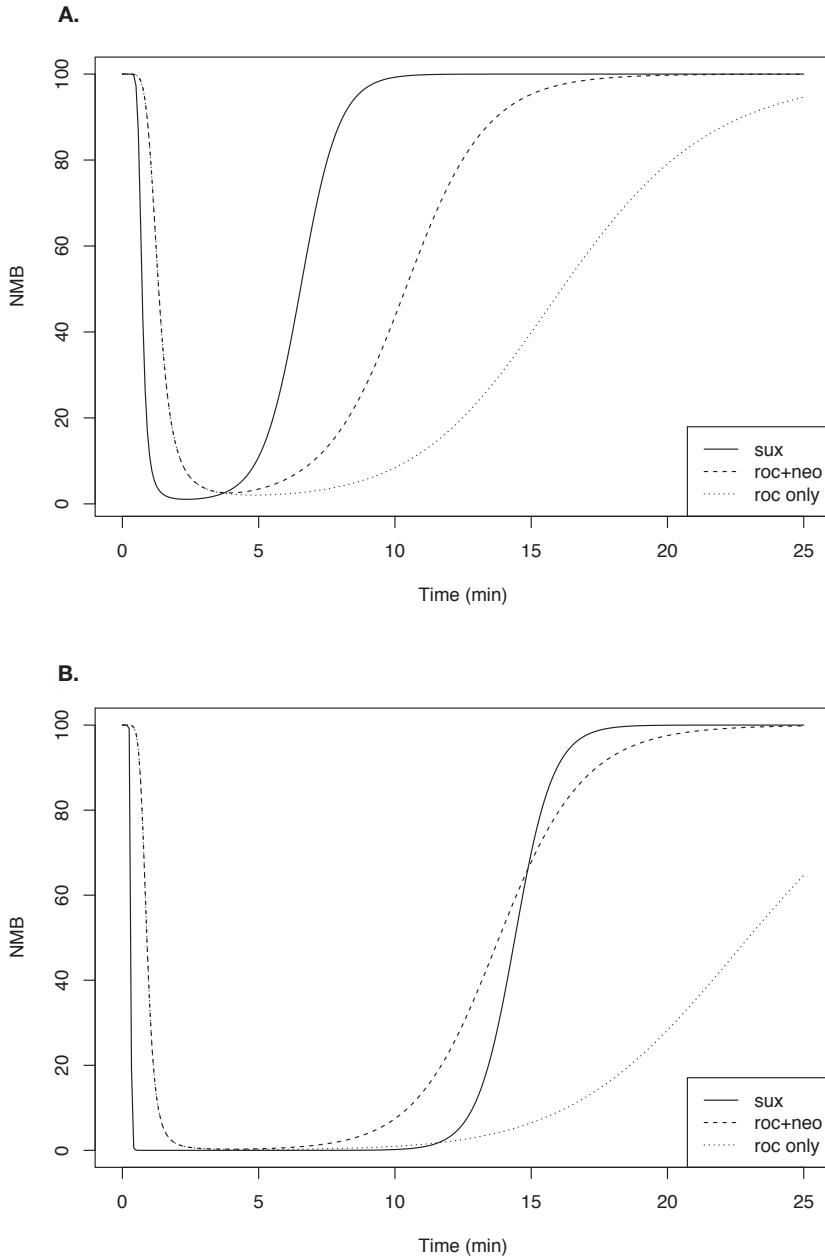


Figure 4A and B. The plots demonstrate the population simulation results for the succinylcholine and rocuronium/neostigmine studies. In the figure A, the doses are assumed to be 0.8 mg/kg and 0.4 mg/kg for succinylcholine and rocuronium. These doses are approximately the minimal effective doses that resulted in the acceptable induced seizure during ECT in 50% of subjects (OED50). In figure B, these doses are assumed to be 1.1 mg/kg and 0.54 for succinylcholine and rocuronium, respectively. These doses are 95 percentile of minimal effective doses (OED95) resulted in acceptable induced seizure during ECT.

DISCUSSION

The half-life of transport between the plasma and effect compartment ($t_{1/2}k_{e0}$, time for effect site concentration to reach to 50% of concentration when the plasma concentration is constant) for succinylcholine at adductor pollicis in this study was almost 5 times that of rocuronium. Onset time of neuromuscular blocking drugs is determined by the time required for drug concentrations at the site of action to reach a critical level, usually that corresponding to 95% block. Onset time is longer than time to peak plasma concentrations. The faster equilibration between plasma concentrations of succinylcholine (higher $t_{1/2}k_{e0}$ \rightarrow lower k_{e0}) at adductor pollicis results in more rapid onset of blockade in adductor pollicis than rocuronium, as shown in this study.

Our succinylcholine k_{e0} estimation in this study is consistent with finding by Roy et al.⁴

The authors reported the estimate k_{e0} of 0.058 for succinylcholine. Considering their reported standard error estimate (SEE) of 0.026, our measured k_{e0} of 0.04 is a reasonable measure of k_{e0} . Furthermore our measured Ce50 of succinylcholine “the effect-site concentration associated with 50% maximal drug effect” being $0.706 \text{ ug/ml} \pm 0.06$, is comparable to the Roy et al.’s estimate of this measurement (0.734 ± 0.211).

Plaud et al.¹⁶ investigated the rocuronium neuromuscular blocking effect (a 5-min infusion) along with neostigmine for its reversal on twitch height in adductor pollicis and estimated the parameters of the rocuronium pharmacokinetics in relation to pharmacodynamics according to Sheiner model¹⁷, i.e., the rate constant of transport between the plasma and effect compartments (k_{e0}) and the concentration producing 50% block (Ce50). They used a two-compartmental pharmacokinetic model. These measured estimates in their study were $0.168 \pm 0.06 \text{ min}^{-1}$ and $0.823 \pm 0.16 \text{ ug/ml}$ for k_{e0} and Ce50. While the estimate of k_{e0} in our study ($0.19 \pm 0.19 \text{ min}^{-1}$) is comparable to Plaud et al.’s report, the Ce50 estimate in our study is two times of the measure ($1.6 \pm 0.1 \text{ ug/ml}$) by these authors. The effect of increasing cardiac output (CO) on the tissue clearance or distribution rate has already been shown, at least when tissue uptake is perfusion limited, as is the case with rocuronium.¹⁸ ECT is associated with a more prominent sympathomimetic activity and an increase in CO.¹⁹ This fact might explain higher estimated rocuronium Ce50 and subsequent the faster recovery times measured by T1 measurement in adductor pollicis that were observed in this study and ECT procedure as compared to the previous reports.^{13, 20} In earlier study presented in chapter three, we also reported longer duration of induce seizure in patients who received rocuronium as NMBA. Other investigators have reported this observation, as well.¹ This observation might be another factor that potentially has affected the concentration of rocuronium in the effect

compartment. Our measured k_{e0} and $t_{1/2}k_{e0}$ for rocuronium is also consistent with the findings by Weirda et al. (0.16 and 3.85 min, respectively).¹³ Cortinez et al. also measured the k_{e0} of rocuronium using both parametric and non-parametric approaches. In both methods the estimated k_{e0} was similarly 0.19 min⁻¹.²¹ However, the measured Ce50 in their study was 0.92 ug/ml. Kuipers et al.¹⁸ showed that the CO could affect some pharmacokinetics parameters and recommended using recirculatory pharmacokinetic model instead of compartmental models to include the CO effect, a matter that should be investigated in an appropriately designed ECT study.

Similar to other studies that investigated PK-PD parameters of neuromuscular blocking agents, we identified higher k_{e0} and lower EC50 for succinylcholine as compared to rocuronium. The onset time for a neuromuscular blocking agent will clinically vary according to factors such as the type of anesthesia, applied dose, type of stimulation for monitoring of neuromuscular blockade (single twitch vs. train-of-four response), and the clinical endpoint used for onset time determination (peak effect or fixed degree of twitch depression) during neuromuscular monitoring.²² Due to crossover design of our study, most of these factors were the same for both succinylcholine and rocuronium, except the applied doses that were increased or decreased to identify the minimal effective dose of each of the NMBA for inducing acceptable neuromuscular block during ECT.

The first order plasma–effect-site equilibration rate constant (k_{e0}) values might vary due circulatory factors that may, in turn alter the onset of action of a NMBA.²² Under identical clinical settings in our study for both succinylcholine and rocuronium, the inter-individual variations in k_{e0} could explain the observed differences in the onset times and recovery times from both of the neuromuscular blockers.

The effect of drug potency in the onset of action of a neuromuscular blocking agent has been supported by several experimental studies such that there is an inverse relationship between onset times and molar potency (ED50) of NMBAs in anaesthetized patients.^{23,24} Consistent with other investigations with applied kinetic-dynamic model²⁵, our pharmacokinetic analysis supports the observation in onset of action for succinylcholine and rocuronium and according to these two NMBA's ED50s (figure 4A).

A higher rate constant for equilibration of the effect compartment concentration with plasma concentration (k_{e0}) and a rapid clearance after a single bolus dose of succinylcholine (recovery from block starts from distribution phase²⁶) as shown in our study (figure 4A and B) has made this drug as the first choice of NMBAs for ECT. The comparison of figures 4A and 3B, derived from population analysis using NONMEM shows the increase of the applied

doses (ED95) of the succinylcholine (from 0.8 mg/kg \approx 2.67 ED95 to 1.1 mg/kg \approx 3.67 ED95) and rocuronium (from 0.4 mg/kg \approx 1.33 ED95 to 0.54 mg/kg \approx 1.8 ED95) decreases the onset of actions and increases the recovery times for both NMBAs. However, the difference in predicted recovery times decreases for the applied doses of 1.1 mg/kg vs. 0.54 mg/kg for succinylcholine and rocuronium/neostigmine, respectively. This observation suggests that in subjects in need of higher doses of succinylcholine for inducing NMB during ECT (approximately > 1 mg/kg), the recovery times might be comparable to induced NMB using rocuronium 0.5-0.6 mg/kg reversed by neostigmine 0.04-0.05 mg/kg.

There are limitations in interpretation of the results of our study to be considered. We did not measure the timely levels of NMBAs in blood after injection and during ECT. Another limitation of the study is inability to measure the neostigmine k_{eo} , in spite of the fact that we estimated neostigmine Ce50 and its effect on the reversal of rocuronium.

In this study, we identified similar pharmacokinetic-pharmacodynamic parameters (k_{eo} and Ce50) for succinylcholine during ECT as previously investigated. For rocuronium the estimated k_{eo} is consistent with others' finding, while we identified higher Ce50 at adductor pollicis that might justify the faster observed recovery from rocuronium induced NMB in this study. This observation warrants further investigation for PK-PD investigation of rocuronium during ECT in a prospective clinical trial.

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